

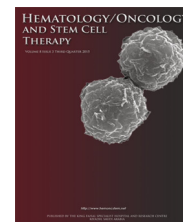


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/hemonc

CASE REPORT

Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection

Neha R. Patil ^{a,*}, Erica S. Herc ^b, Marian Girgis ^a^a Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Health System, Wayne State University, Detroit, MI, USA^b Division of Infectious Disease, Department of Internal Medicine, Henry Ford Health System, Wayne State University, Detroit, MI, USA

Received 12 May 2020; received in revised form 1 June 2020; accepted 14 June 2020

KEYWORDS

Anemia;
Autoimmune;
Cold agglutinin disease;
COVID-19;
Hemolytic;
Pulmonary embolism

Abstract

Background: Lymphopenia, thrombocytopenia, and elevated D-dimer and ferritin levels are frequently reported in patients with severe coronavirus disease 2019 (COVID-19). Here we report a case of cold agglutinin disease (CAD), autoimmune hemolytic anemia (AIHA), and pulmonary embolism as a presentation of COVID-19 infection.

Case report: A 51-year-old African–American woman presented to the emergency room with fever and shortness of breath. She was tachycardic, febrile, and had an oxygen saturation of 88% on room air. Laboratory studies showed hemoglobin (Hb) 5.1 g/dL, D-dimer 4.55 µg/mL, and C-reactive protein 12.3 mg/dL. Computed tomography scan of the chest showed acute pulmonary embolism involving the bilateral lower lobe segmental branches. Her influenza test was negative, but her SARS-CoV-2 test returned positive. Due to severe anemia, she was not started on any anticoagulation. Haptoglobin was low. Direct antiglobulin test returned positive for anti-complement and negative for anti-immunoglobulin G. Cold agglutinin titer was 80. Mycoplasma, Epstein–Barr virus, parvovirus, human immunodeficiency viruses, and acute hepatitis screen were negative. Abdominal and pelvic computed tomography showed a normal liver and spleen without lymphadenopathy. Peripheral blood smear showed red blood cell agglutination. On Day 2, she became hypoxic requiring 6 L oxygen. Since her Hb remained

* Corresponding author at: Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Health System, Wayne State University, 2799 West Grand Boulevard, CFP 555, Detroit, MI 48202, USA.

E-mail address: npatil321@gmail.com (N.R. Patil).

<https://doi.org/10.1016/j.hemonc.2020.06.005>

1658-3876/© 2020 King Faisal Specialist Hospital & Research Centre. Published by Elsevier Ltd.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Please cite this article as: N. R. Patil, E. S. Herc and M. Girgis, Cold agglutinin disease and autoimmune hemolytic anemia with pulmonary embolism as a presentation of COVID-19 infection, *Hematol Oncol Stem Cell Ther*, <https://doi.org/10.1016/j.hemonc.2020.06.005>

stable, she was started on low-intensity unfractionated heparin. Inflammatory markers subsequently improved and she was weaned off oxygen. Her Hb remained stable at 9 g/dL and she was discharged home. After 2 weeks, her Hb increased to 11 g/dL.

Conclusion: As exemplified in this case report, COVID-19 infection can lead to thromboembolism, CAD, and AIHA and it should be recognized as a potential etiology to such rare diseases.

© 2020 King Faisal Specialist Hospital & Research Centre. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the strain that causes coronavirus disease 2019 (COVID-19). While most patients have mild disease, some develop severe disease. Comorbidities including chronic lung disease, diabetes, malignancy, immunosuppression, and obesity, and the elderly are at higher risk of severe outcomes.

Lymphopenia, thrombocytopenia, and elevated D-dimer and ferritin levels are frequently associated with severe disease [1–3]. Disseminated intravascular coagulation [4] and venous thromboembolism (VTE) [5] have also been reported.

We report a case of cold agglutinin disease (CAD), autoimmune hemolytic anemia (AIHA), and pulmonary embolism (PE) as a presentation of COVID-19 infection at our institution.

CAD is very rare with a prevalence of 16 cases per million persons. In CAD, extravascular hemolysis causes acute hemolytic anemia where agglutination of red blood cells occurs at below normal core body temperature [6,7].

The two main types of CAD are primary (idiopathic) and secondary. Secondary CAD is associated with viral infections, autoimmune disorders, and hematologic malignancies. The most common infectious causes associated with CAD are *Mycoplasma pneumoniae* and Epstein–Barr virus [7,8]. Patients may develop hemolysis 2 weeks after the initial infection. Laboratory abnormalities typically improve with resolution of infection [7,9].

Case report

Our patient is a 51-year-old African–American woman with a past medical history of right breast ductal carcinoma *in situ* diagnosed in 2012 status post lumpectomy, radiation and tamoxifen for 2 years. She was diagnosed with recurrent stage IA right breast cancer in 2019 and underwent a nipple-sparing mastectomy on January 16, 2020, with breast reconstruction on February 26, 2020. She also has a history of left lower extremity VTE in her 30s provoked by oral contraceptive pills.

The patient presented to the emergency room on March 28, 2020, with fever, shortness of breath, malaise, rib, and back pain. In the emergency room, she was tachycardic with a heart rate of 112 beats/minute and febrile with 102.2°F. She had an oxygen saturation of 88% on room air. Laboratory studies were notable for white blood cell count of 12,000 K/ μ L, absolute lymphocyte count 2.10 K/ μ L, hemoglobin (Hb) 5.1 g/dL down from baseline of 12 g/dL, indirect bilirubin

2.2 mg/dL, D-dimer 4.55 μ g/mL, lactate dehydrogenase 518 IU/L, ferritin 1418 ng/mL, C-reactive protein (CRP) 12.3 mg/dL, haptoglobin < 30 mg/dL, platelets 303 K/ μ L, and fibrinogen 534 mg/dL; prothrombin time, partial thromboplastin time, and international normalized ratio were within normal limits. She denied any bleeding. She received 2 units of packed red blood cells in the ER.

Computed tomography scan of the chest showed acute PE involving the bilateral lower lobe segmental branches. Dependent airspace disease in the posterior lower lobes related to atelectasis and/or pneumonia was also seen. There was also concern for breast surgical site infection from her recent breast reconstruction. She was admitted for sepsis management. Influenza test was negative, but her SARS-CoV-2 test returned positive. Due to severe anemia, she was not started on full-dose anticoagulation in the ER. The Infectious Disease Service was consulted, and she was started on hydroxychloroquine.

Anemia workup including vitamin B12 level and folate level were normal. Antinuclear antibody and rheumatoid factor were negative. Monoclonal protein evaluation showed an inflammatory pattern. Glucose-6-phosphate-dehydrogenase level was normal. *Mycoplasma*, Epstein–Barr virus, parvovirus, human immunodeficiency viruses, and acute hepatitis screen were negative. Occult blood stool test was negative. Abdominal and pelvic computed tomography showed a normal liver and spleen without lymphadenopathy.

Direct antiglobulin test returned positive. Anti-immunoglobulin G Coombs serum was negative and anti-complement was positive. Cold agglutinin titer was 80. Peripheral blood smear showed red blood cell agglutination. As her workup was consistent with CAD and cold AIHA, we started her on folic acid and recommended to use warm intravenous fluids and blood products.

On Day 2, she became more hypoxic requiring 6 L oxygen and was started on solumedrol 60 mg twice daily. Her Hb remained stable, and she was started on low-intensity unfractionated heparin without boluses for PE with close monitoring of her Hb. By Day 4, her D-dimer and ferritin levels increased to 7.54 μ g/mL and 1471 ng/mL, respectively.

Inflammatory markers subsequently improved. CRP decreased to 0.7 mg/dL, and she was weaned off oxygen. Her Hb remained stable at 9 g/dL, and she was discharged home in a stable condition. After 2 weeks of hospital discharge, her Hb increased to 11 g/dL. The WBC count was 6 K/ μ L with normal absolute neutrophil and lymphocyte counts.

Discussion

The COVID-19 pandemic has caused significant morbidity and mortality. We are still in the process of understanding its pathogenesis, clinical manifestations, management, and prognosis.

High D-dimer levels and coagulopathy have been frequently reported in patients with severe disease. The prevalence of VTE in hospitalized patients with COVID-19 is 25–31% [5,10]. A study of 81 hospitalized patients with COVID-19 showed that 25% developed VTE. Of those, eight/20 patients died [10]. Klok et al. [5] reported regarding 84 patients with COVID-19 admitted in the Dutch university hospital who received thromboprophylaxis. The cumulative incidence of thrombosis was 31% (95% CI = 20–41). PE was the most frequent complication (81%) [5].

The International Society of Thrombosis and Hemostasis guidelines now recommend prophylactic-dose anticoagulation in all hospitalized patients with COVID-19 [11]. Some centers are now considering therapeutic-dose anticoagulation in patients with severe COVID-19, especially those with high D-dimer levels and coagulopathy.

Our patient had elevated levels of D-dimer (7.45 µg/mL), ferritin (1471 ng/mL), and CRP (12.3 mg/dL) at presentation, which were concerning for ongoing inflammation. There was no obvious provoking factor to her PE, and thus it was attributed to her COVID-19 infection.

With prompt COVID-19 and PE management using hydroxychloroquine, solumedrol, and heparin, our patient's inflammatory markers and clinical condition improved in a few days. CRP decreased to 0.7 mg/dL (previously 12.3 mg/dL), she was weaned off oxygen (6 L to room air), and her Hb remained stable (9 g/dL) while in the hospital and increased to 11 g/dL at follow-up.

To our knowledge, this is the first case report of CAD with AIHA secondary to SARS-CoV-2 infection. Her workup for other etiologies including other viral and autoimmune studies was unrevealing. Her cold agglutinin titer was elevated at 80.

The management of her case was challenging as anticoagulation was held initially in the setting of severe anemia of Hb of 5.1 g/dL. Once bleeding was ruled out and her Hb remained stable after transfusion and with folic acid supplements, we implemented anticoagulation with low-intensity unfractionated heparin protocol and monitored her Hb every 8 h to ensure stability for 24 h.

Complete blood count with differential, D-dimer, coagulation studies, CRP, and ferritin should be assessed in all hospitalized patients with COVID-19. Hematologic abnormalities need close monitoring and prompt intervention if these parameters worsen. Hospitalized patients with severe COVID-19 are at high risk for VTE, disseminated intravascular coagulation, and subsequent mortality. Although bleeding complications are rare with COVID-19, bleeding risk needs to be considered on an individual basis.

Management of CAD includes cold avoidance, maintaining Hb at acceptable level, and treating underlying autoimmune, infectious, or bone marrow disorder. CAD commonly presents with hemolysis which could range from a mild form without anemia and compensated to a severe form requiring transfusions. Cold AIHA secondary to viral infections usually

occurs within 2 weeks of the onset of primary infection and improves by the time of infection resolution.

In severely ill hospitalized patients, plasmapheresis or intravenous immunoglobulin can be used as a temporizing measure in addition to blood transfusion. Treatment is aimed at reducing antibody production. Patients with CAD due to infections usually have polyclonal cold agglutinin. Steroids are generally not effective.

Rituximab alone or in combination with bendamustine is usually administered to patients with chronic CAD, with or without underlying lymphoproliferative disorder [12]. These patients usually have a monoclonal cold agglutinin; thus, directed therapy against the clone of B cells or antibody-producing plasma cells is usually effective.

Rituximab is an anti-CD20 monoclonal antibody. It causes lymphopenia in about 48% of patients at a median of 14 days [13,14]. Thrombocytopenia, anemia, hypogammaglobulinemia, and prolonged neutropenia are also seen [15,16]. Most hospitalized patients with COVID-19 already have lymphopenia and thrombocytopenia. Therefore, administering rituximab to patients with COVID-19 may be risky because it can cause further B-cell depletion and can increase their risk for acquiring other infections.

Conclusion

Hematologic manifestations of COVID-19 infection remain to be completely defined. Our patient presented with CAD and AIHA in the setting of SARS-CoV-2 infection. SARS-CoV-2 should be recognized as a possible viral etiology to such rare diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
- [2] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
- [3] Fan BE, Chong VC, Chan SS, Lim GH, Lim KG, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. *Am J Hematol* 2020;95:E131–4.
- [4] Deng Y, Liu W, Liu K, Fang YY, Shang J, Zhou L, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *Chin Med J* 2020;133:1261–7.
- [5] Klok FA, Kruip MJ, Van der Meer NJ, Arbous MS, Gommers DA, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–7. <https://doi.org/10.1016/j.thromres.2020.04.013>.
- [6] Berentsen S, Ulvestad E, Langholm R, Beiske K, Hjorth-Hansen H, Ghanima W, et al. Primary chronic cold agglutinin disease: a

- population based clinical study of 86 patients. *Haematologia* 2006;91:460–6.
- [7] Berentsen S, Tjønnfjord GE. Diagnosis and treatment of cold agglutinin mediated autoimmune hemolytic anemia. *Blood Rev* 2012;26:107–15.
- [8] Randen U, Trøen G, Tierens A, Steen C, Warsame A, Beiske K, et al. Primary cold agglutinin-associated lymphoproliferative disease: a B-cell lymphoma of the bone marrow distinct from lymphoplasmacytic lymphoma. *Haematologica* 2014;99:497–504.
- [9] Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. *Am J Hematol* 2002;69:258–71.
- [10] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 2020;18:1421–4. <https://doi.org/10.1111/jth.14830>.
- [11] Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020;18:1023–6.
- [12] Berentsen S. How I manage patients with cold agglutinin disease. *Br J Haematol* 2018;181:320–30. <https://doi.org/10.1111/bjh.15109>.
- [13] Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. *Drugs* 2003;63:803–43.
- [14] Cattaneo C, Spedini P, Casari S, Re A, Tucci A, Borlenghi E, et al. Delayed-onset peripheral blood cytopenia after rituximab: frequency and risk factor assessment in a consecutive series of 77 treatments. *Leuk Lymphoma* 2006;47:1013–7.
- [15] Makatsori M, Kiani-Alikhan S, Manson AL, Verma N, Leandro M, Gurugama NP, et al. Hypogammaglobulinaemia after rituximab treatment-incidence and outcomes. *QJM* 2014;107:821–8.
- [16] Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. *Medicine* 2010;89:308–18.